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INVITED EDITORIAL
Polymorphisms in Drug-Metabolizing Enzymes: What Is Their Clinical Relevance and Why Do They Exist?

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The beautiful report by Sachse et al. (1997) in this issue of the *Journal* represents the culmination of 2 decades of increasingly exciting work on the "debrisoquine oxidation polymorphism," one of dozens of *pharmacogenetic* or *ecogenetic* polymorphisms that have been shown to have an important impact on innumerable clinical diseases. *Pharmacogenetics* is the study of the hereditary basis of the differences in responses to drugs. *Ecogenetics* is the broader field of interindividual differences in response to all environmental chemical and physical agents (e.g., heavy metals, insecticides, compounds formed during combustion, and UV radiation). It is now clear that each of us has his or her own "individual fingerprint" of unique alleles encoding the so-called drug-metabolizing enzymes (DMEs) and the receptors that regulate these enzymes.

In this invited editorial, I first introduce the current thinking in the field of DME (and DME-receptor) research and how DMEs have evolved from animal-plant interactions. I then describe the debrisoquine oxidation polymorphism, as well as two other relevant DME polymorphisms; show the relationship between these polymorphisms and human disease; provide examples of synergistic effects caused by the combination of two DME polymorphisms; and discuss the ethical considerations of such research. Last, I speculate on why these allelic frequencies of the DME genes might exist in human populations in the first place.

Phase I and Phase II DMEs

Several dozen human DME genetic polymorphisms have been characterized (Nebert and Weber 1990; Gonzalez and Idle 1994; Kalow and Bertilsson 1994; Nebert et al. 1996). Although some of these have been shown quite convincingly to be correlated with enhanced risk of toxicity or cancer, others presently remain equivocal. It has been estimated that, whereas approximately three-fourths of drugs and other environmental chemicals are toxic in their nonmetabolized parent forms (e.g., isoniazid and dioxin), the remaining one-fourth of DME substrates (e.g., acetaminophen and benzene) are metabolically potentiated to toxic or mutagenic intermediates. Phase I DMEs, most of which represent cytochromes P450, metabolically activate procarcinogens to genotoxic (DNA-damaging) electrophilic intermediates. Phase II DMEs (such as UDP glucuronosyltranferases, glutathione transferases, and N-acetyltransferases) conjugate the intermediates to water-soluble derivatives, completing the detoxification cycle. Hence, it seems obvious that genetic differences in the regulation, expression, and activity of phase I and phase II DME genes might be crucial factors in defining cancer susceptibility, as well as in determining the toxic or carcinogenic power of drugs and other environmental pollutants.

DMEs and Their Receptors as Involved in Critical Life Functions

Between 1950 and 1970, DMEs usually were described as "liver detoxification systems" that were responsible for the degradation of drugs and other environmental pollutants in order to aid in their excretion. This dogma is still being widely taught, although "drug detoxification" probably represents <1% of all DME functions—if one considers the following facts. (*a*) All DMEs have endogenous compounds as their natural substrates. (*b*) DMEs are involved in the synthesis and degradation of every known nonpeptide involved in ligand-modulated transcription processes (including second-messenger pathways) that cause growth, differentiation, apoptosis, homeostasis, and neuroendocrine functions. For example, vitamin D_3 25-hydroxylase and 25-hydroxy-D_3 1α-hydroxylase are required for formation of the most potent ligand for the vitamin D receptor (VDR), whereas the 25-hydroxy-D_3 24-hydroxylation and 1α,25-dihydroxy 24-hydroxylation pathways produce an inactive VDR ligand (Nebert and McKinnon 1994). Cyclooxygenase, leukotriene C_4 synthase (a glutathione transferase), thromboxane synthase (CYP5),

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and prostacyclin synthase (CYP8) represent four of the many DMEs that participate in the arachidonic acid cascade. (*c*) Numerous DMEs existed in evolution prior to the divergence of eubacteria from eukaryotes—suggesting that these enzymes were responsible for important life functions (e.g., calcium ion and electrolyte balances, cell division, and mating) long before animal-plant divergence or the establishment of pharmacies and drug stores. (*d*) At least some DMEs are located in every eukaryotic cell. Given these connections, a more appropriate name for DMEs therefore might be "effector-metabolizing enzymes" (Nebert 1990, 1991*c*, 1994).

All "DME receptors" (e.g., estrogen receptor [ER], peroxisome proliferator–activated receptor [PPAR], and dioxin-binding Ah receptor [AHR]) undoubtedly have existed for hundreds of millions of years in order to carry out critical life functions involving known—or as-yet-unestablished—endogenous ligands. Foreign chemicals are able to bind to these receptors and act as agonists or antagonists—which then can result in toxicity and cancer (Nebert 1994). For example, estrogen, diethylstilbestrol, tamoxifen, kepone, and *p,p'*-DDT [1,1'-(2,2,2-trichloroethylidene)*bis*(4-chlorobenzene)] are all potent ligands for the ER.

Animal-Plant "Warfare" and/or Cooperation

There is ample evidence that the evolution of DME genes and DME receptor genes in animals has occurred because of the interaction of animals with plants (e.g., requirement for food and reproductive cycles). The evolution of plant secondary metabolites (e.g., flower pigments; odorants that either attract or repel pollinators and predators; and phytoalexins having antimicrobial, antifungal, insecticidal, or antiviral activity) has occurred because plants need animals for their reproductive cycles but also must maintain defense systems for survival (Gonzalez and Nebert 1990). For example, there was an "explosion" of new animal cytochrome P450 genes in the *CYP2* family (Nelson et al. 1996)—evidence of >50 gene-duplication events starting ~400 million years ago when animals first came onto land and began ravaging stationary terrestrial plant forms. Presumably, plants had to defend themselves by evolving new genes (and thus new metabolites) to make them less palatable or more toxic, and animals responded by evolving new DME genes in order to adapt to the constantly changing plants (Gonzalez and Nebert 1990).

Because of the coevolution of plants and animals, plant metabolites have evolved in response to both the biochemical susceptibilities and the capabilities of animals. Plants that depend on animals for seed dispersal might exhibit two different and opposing constraints on their synthesis of toxic metabolites: too little, and the animals win; too much (or too toxic—or too broad in spectrum), and the animals will die or be repulsed or both. Conversion of a pine-tree terpene by the bark beetle to an inhibitor of pheromone attraction (Byers 1983), release of an alarm pheromone by the wild potato to repel aphids (Gibson and Pickett 1983), and a toxic phenol in winter-dormant foliar buds of the green alder to deter snowshoe hare feeding (Bryant et al. 1983) are examples of how plants can repulse animal predators. Potent antifungal agents can evolve in plants in order to defend the latter from invading fungi (Petranyi et al. 1984). The coevolution of rootworm beetles with plants of the family Cucurbita (Metcalf and Lampman 1991) and of attine (leaf-cutting) ants and their fungal symbionts (Hinkle et al. 1994) are examples of animal-plant cooperation over hundreds of millions of years.

If the response of the predator to a plant metabolite is weak, the plant might be able to potentiate the response by making another metabolite that acts synergistically. For example, chocolate has both a compound that binds to the CNS receptor for anandamide (an endogenous molecule mimicked by plant-derived cannabinoids) and an activity that blocks the catabolism of cannabinoids. Providing a ligand, as well as blocking ligand degradation, thus produces a synergistic effect (di Tomaso et al. 1996), which is proposed to account for the craving that many people have for chocolate.

The synthesis and degradation of plant metabolites by animal DMEs undoubtedly have evolved to the present-day metabolic activation and detoxification of innumerable environmental pollutants, carcinogens, and drugs. For example, CYP6B1, a P450 enzyme in the black swallowtail butterfly, allows its larvae to feed on furanocoumarins (which repel most insects) of the carrot and citrus families (Berenbaum and Feeny 1981; Ma et al. 1994). The entire field of pharmacology and drug development represents the discovery and characterization of naturally occurring plant metabolites—and of synthetic analogues that are found to do a better job with fewer side effects. There are implications of such "unnatural selection," which would apply to prospective synthetic drugs. A newly designed drug, having fewer undesirable side effects, might be detoxified or metabolically potentiated by humans more rapidly (or slowly) or might bind, with higher (or lower) affinity, to its receptor(s) or cell type–specific coactivator(s), corepressor(s), or other receptor-associated protein(s). As unequivocal genotyping tests for DME gene (and DME receptor) polymorphisms are developed, identification of individuals at increased risk of cancer and toxicity (including idiosyncratic drug responses) would be extremely valuable in the fields of public health, risk assessment, and preventive medicine.

The *CYP2D6* Plymorphism

The elegant work of Robert L. Smith uncovered the debrisoquine oxidation polymorphism 2 decades ago

(Idle and Smith 1979). Smith noticed that the antihypertensive agent debrisoquine—released on the British pharmaceutical market but never approved in the United States—caused an unexpectedly high incidence of side effects ("idiosyncratic drug reactions"). Smith reasoned that an underlying genetic variation in the way in which individual patients metabolize the drug might be responsible for this high incidence of undesirable responses. Smith and three laboratory colleagues took the prescribed dose and measured the levels of metabolites in their urine. Besides becoming hypotensive himself—from ingesting the "recommended" dosage of debrisoquine—Smith found that his urinary 4-hydroxy metabolite was ~20-fold less than that of his three colleagues!

A larger population was screened. Poor metabolizers (PMs) of debrisoquine were found to represent 6%–10% of Caucasian populations, as compared with extensive metabolizers (EMs), who handle the drug 10–200 times more efficiently. PM frequencies are ~5% in Black populations and <1% in Asians. The DME was shown to be a cytochrome P450 and was named "CYP2D6." PM alleles code for a defective protein and/or incorrect splicing of the gene transcript—resulting in lowered or completely absent enzyme activity. The *CYP2D6* gene was localized to chromosome 22q13.1, near the *SIS* oncogene. Interestingly, an "ultrarapid metabolizer" phenotype has also been found—and shown to be due to amplification of the *CYP2D6* gene as many as 12 times (Meyer 1994). A unified nomenclature system for the human *CYP2D6* alleles recently has been proposed (Daly et al. 1996).

The Sachse et al. study in this issue of the *Journal* describes the development of a nested-PCR-RFLP test from a PCR amplification of the entire *CYP2D6* gene. This test is able to detect the *CYP2D6*1* (EM) "wild-type" allele and >16 PM alleles—including three novel variants. Genotyping 589 unrelated volunteers, the Sachse et al. study provides one of the largest screenings yet for determining *CYP2D6* allelic frequencies.

The "*CYP2D6* Panel"

Many prescribed drugs, as well as over-the-counter drugs, are processed by the same enzyme. The "debrisoquine panel" now comprises >30 drugs and environmental chemicals—including antiarrhythmics, antihypertensives, β-blockers, monoamine oxidase inhibitors, morphine derivatives, antipsychotics, and tricyclic antidepressants (Nebert 1991*a*, 1991*b*; Gonzalez and Idle 1994; Meyer 1994). In fact, the *CYP2D6* polymorphism may be important in the handling of as much as 20% of all commonly prescribed drugs. Moreover, it is noteworthy that—although humans probably have ~60 unique P450 genes (Nelson et al. 1996)—only approximately a half dozen (CYP1A2, CYP2C17, CYP2D6, CYP2E1, CYP3A4, and CYP4A11) appear to be responsible for metabolism of the vast majority of prescribed and over-the-counter drugs. The day might not be too distant that selection of drugs, as well as dosage of drugs, could be adjusted principally on the basis of knowing the individual's genotype instead of on the basis of monitoring plasma drug concentrations or of waiting for favorable therapeutic responses or idiosyncratic reactions to occur.

Association of the *CYP2D6* Phenotype and Disease

Numerous epidemiological studies linking the *CYP2D6* allelic differences with toxicity and cancer have been reported. The majority of studies suggest that the EM phenotype might be associated with an increased incidence of malignancies of the bladder, liver, pharynx, and stomach—and, especially, cigarette smoking–induced lung cancer. These data suggest that enhanced CYP2D6-mediated metabolism of one or more unknown dietary and other environmental agents, to form a reactive intermediate (phase I effect), might play a role in cancer initiation and/or promotion in the above-named tissues.

Individuals with the PM phenotype also appear to have a 2–2.5-fold increased risk of developing Parkinson disease (Nebert and McKinnon 1994). A possible relationship between the PM phenotype and decreased tolerance to chronic pain has been suggested to reflect differences in the endogenous synthesis of morphine by CYP2D6 in the human brain. Studies attempting to show an association between the CYP2D6 phenotype and the tendency to opiate addiction are underway in several laboratories. At least two studies have implicated a relationship between CYP2D6 and dopamine neurotransmission in the brain. Even differences between EM and PM individuals' personalities have been reported, suggesting further that CYP2D6 might metabolize substances critical to CNS function (Kalow and Bertilsson 1994).

N-Acetylation Polymorphism

A second example of a DME polymorphism, the "isoniazid acetylation polymorphism," first was identified in the late 1940s when tuberculosis patients routinely were being given isoniazid. A high incidence of peripheral neuropathy was described and found to represent the unusually slow clearance of the toxic parent compound, isoniazid. Subsequently, individuals were phenotyped as "slow" or "rapid" acetylators. The slow-acetylator phenotype was found to be inherited as an autosomal recessive trait, and 40%–60% of Caucasians are homozygous for the slow-acetylator alleles. Worldwide, the frequency of the slow-acetylator phenotype

ranges from ~10% in the Japanese to >90% in some Mediterranean populations.

Two human N-acetyltransferase functional genes (*NAT1* and *NAT2*) and one pseudogene (*NATP*) have been cloned and localized to chromosome 8pter-q11. The rapid- and slow-acetylator phenotype was found to involve principally the *NAT2* gene, encoding the NAT2 enzyme, which has a 10-times-lower K_m for aromatic amines than does NAT1 (although an *NAT1* polymorphism now has been described also). Three major slow-acetylator *NAT2* alleles (two common in Caucasians and one common in Asians) have been identified, and the number of minor, rare *NAT2* alleles is now >20 (Gonzalez and Idle 1994; Vatsis et al. 1995; Nebert et al. 1996).

The *NAT2* Polymorphism and Human Disease

Epidemiological associations between the acetylation phenotype and cancer or toxicity have been studied extensively. The slow acetylators were found to exhibit less risk of colorectal carcinoma but a higher risk (odds ratio 16.7) of bladder cancer (Gonzalez and Idle 1994). Cigarette smoking and occupational exposure to arylamines are important factors, in conjunction with the slow-acetylator phenotype, for development of bladder cancer. No relationship was found between acetylator phenotype and smoking-related bladder cancer in the absence of exposure to arylamines. Very recently, cigarette-smoking postmenopausal women with the slow-acetylator phenotype have been shown to be as much as fourfold more likely to develop breast cancer than are those with the rapid-acetylator allele (Ambrosone et al. 1996). Toxic nitrosamines in tobacco smoke, which are degraded by NAT2 more slowly over many years, might cause the individual to be more susceptible to breast cancer.

Slow acetylators are also more prone to develop hydralazine- or procainamide-induced lupus syndrome, as well as to suffer from hemolytic anemia caused by certain sulfonamides. Systemic lupus erythematosus occurs predominantly among slow acetylators, suggesting that the slow metabolism of one or more unknown dietary or other environmental substances over many years could provoke the disease.

Glucose-6-Phosphate Dehydrogenase (G6PD) Polymorphism

This polymorphism is relevant to pharmacogenetics and ecogenetics because G6PD is crucial in the maintenance of reduced glutathione (GSH) levels—important in phase II detoxification pathways. The polymorphism was first realized during World War II, when soldiers who were being treated for malaria and who were transported by aircraft at 5,000–10,000-foot altitudes, developed hemolytic anemia crises. Although having the covert disorder of G6PD deficiency, these individuals (most of whom were African Americans, who have ~10% incidence of the A-type G6PD deficiency) exhibited symptoms only when the G6PD pathway was challenged by the combination of the antimalarial drug primaquine and the lowered oxygen tension in their red blood cells.

G6PD is an enzyme in the hexose monophosphate shunt—one of the principal sources of NADPH generation (leading subsequently to glutathione synthetase–hormone generation) in the normal red blood cell. The *G6PD* gene is located on the X chromosome. Approximately 10% of the world population has one or another of the >300 different G6PD variants. Ethnic differences can be striking—for example >100-fold between Ashkenazic and Sephardic Jews (Nebert and Weber 1990; Kalow and Bertilsson 1994).

Synergy between Two Ecogenetic Loci

A toxic response to an environmental agent can be exaggerated greatly by the combination of two ecogenetic differences in the same individual. In other words, the total response is much greater than the sum of the two pathways separately. For example, individuals who have high CYP1A2 activity combined with the rapid-acetylator phenotype are able to clear caffeine much more quickly than those having low CYP1A2 activity and the slow-acetylator phenotype.

Another example of synergy is particularly relevant to occupational medicine. Among workers exposed to aniline dyes, hemoglobin adducts were found to be as much as 50 times higher in the G6PD-deficient slow acetylator than in the combined normal-G6PD/rapid acetylator phenotype (Lewalter and Korallus 1985). These intriguing data offer an interesting dilemma to the industrial hygienist, whose job it is to determine exposures in the workplace. Although individuals might be exposed to the same level of a particular occupational chemical or mixture, the risk of an adverse health effect (or simply the measurement of a biomarker presumed to determine the amount of exposure) may vary by two or more orders of magnitude—because of the underlying genetic predisposition of each worker.

Relationship between DME Polymorphisms and Cancer

The *CYP2D6*, *NAT2*, and *G6PD* polymorphisms are just three of several dozen examples, described to date, of the interaction between interindividual genetic predisposition and the environment. For years there has been the raging controversy over whether cancer is caused principally by genetic or environmental factors. The fact that we all have variable metabolic responses to environ-

mental mutagens, carcinogens, and toxicants really serves to undermine any facile distinction between a "pure" genetic or environmental etiology of cancer. Differences in metabolism of dietary and other environmental agents over long periods of time can result in DNA damage or alterations in critical signal-transduction pathways. Obviously, the risk of particular types of cancer will increase with age and will reflect a number of different mechanisms.

Whereas any form of cancer is clearly a multiplex phenotype, it is likely that one or more of the factors contributing to the increased risk of the vast majority of malignancies will be shown to be the DME genes and the receptors controlling DME genes. The same can be said for any other human disease caused by environmental toxicants.

Ethical Considerations

In many cases, our increasing knowledge of pharmacogenetic and ecogenetic differences that can be explained on the DNA level will be advantageous to society; these advantages might be described as "preventive toxicology." For a physician to decide to prescribe one drug in place of another—perhaps thereby avoiding an idiosyncratic drug response—the availability of pharmacogenotyping tests will be very welcome. Patients also would prefer not to have undesirable side effects from a prescribed (or over-the-counter) drug. Workers would prefer not to be overly exposed to occupationally hazardous agents—if they understood that they had a predisposition to cancer or toxicity caused by these agents. Because only 7 of 100 cigarette smokers die of bronchogenic carcinoma, perhaps even some cigarette smokers—who knew that they were genetically prone to developing lung cancer—might avoid smoking (or secondhand smoke) if they were aware of their DME genotype associated with malignancy.

Our increasing knowledge of ecogenetic differences explained on the DNA level could have a dark side, however (Parker 1994). For example, an employer might like to know the genotype of its workers, in order to hire only those at lower risk for toxicity or malignancy from exposure to particular agent(s) in the workplace. Knowledge of the ecogenotype of individuals by medical insurance companies could provide information on which such companies might profit by refusing insurance to "high-risk" persons. For these reasons, it is important to prevent abuse of ecogenotyping information on individuals.

The Purpose of These DME (and DME Receptor) Polymorphisms?

To a geneticist, any time that an allele is found to have a population frequency >.01, it is asked if the allele could have a selective advantage. Why do these poor-metabolizer and slow-acetylator alleles occur at high frequencies in human populations?

Spontaneous mutation rates are generally $1/10^6$ or $1/10^8$. The founder effect, which is the overpropagation of a particular allele because of a genetic "bottleneck," can explain increases in the frequency of a gene in local populations of recent origin. Neither spontaneous mutation nor the founder effect, however, can explain the striking interindividual differences or the geographic differences in DME alleles that I have described above. Some compensating advantage therefore must be suspected. I can think of two possible selective pressures.

First, the striking differences in allelic frequencies in DME genes—seen between ethnic groups—might reflect *differences in diet* that have evolved over thousands of years. Just as is true for all drugs and environmental pollutants, foodstuffs (from which many drugs have been derived) represent DME substrates. As noted earlier, the *CYP2D6, NAT2,* and *G6PD* polymorphisms exhibit dramatic ethnic differences. Differences in the incidence of one phenotype that is shared by ethnic groups can be large; for example, the incidence of G6PD deficiency is 0.4% and 53% in Ashkenazic Jews and Sephardic Jews, respectively (Nebert and Weber 1990).

How long might it take for the human genome to adapt to dietary selective pressures? By means of genetic drift and natural selection (random mutations, gene duplication, crossing-over events, etc.), new genes become fixed and are passed on to the next generation because of an ecologic advantage to the species. It is becoming increasingly appreciated in evolutionary studies that such changes might occur slowly—or might occur rapidly, in just a few generations—depending on the selection pressures. If the population of a species decreases dramatically so that rare variants are more likely to reproduce, the distribution in that population would shift much more rapidly.

The development of individuals within a population that are resistant to changes in their environment has been demonstrated experimentally in various organisms, from prokaryotes (Cairns et al. 1988) and arthropods to mammals, but the mechanisms involved remain basically obscure. Depending on the organism studied, 10–50 generations are required. The "short-sleep" and "long-sleep" mouse lines—developed from heterogeneous stock mice over >20 generations of selective breeding in response to intraperitoneal ethanol (McClearn and Kakihana 1973; Bigelow et al. 1989)—represent an example of molecular drive in mammals. For humans, 10–50 generations would represent a range of 200–2,000 years. Most *Homo sapiens* ethnic groups appear to have diverged from one another during the past 50,000 years (Nei and Saitou 1986). During this time span, it is therefore possible that striking ethnic

differences in DME polymorphisms have arisen from selective pressures that were caused by tribal differences in diet or exposure to other environmental signals. It is very likely, for example, that 6,000 years of a diet principally of goat meat and milk products—compared with that principally of tropical fruits and plants—might lead to DME polymorphisms.

Second, the high allelic frequencies seen in DME genes—between individuals within any one ethnic group—might represent the evolution of *balanced polymorphisms*. The classical example of a compensating, or "shared benefit," polymorphism is the sickle-cell trait: whereas, because of severe anemia, the homozygous carriers of this trait die (or fail to reproduce), the much larger number of heterozygotes resist malaria better than do wild-type homozygotes. Furthermore, it is becoming increasingly appreciated that there are several classes of diseases in which the homozygote bears the risks while the heterozygote is believed to retain a distinct survival advantage: (*a*) resistance to bacterial and viral pathogens, (*b*) improved prenatal survival, and (*c*) improved postnatal survival in response to particular environmental stresses (Rotter and Diamond 1987). Examples of balanced polymorphisms include G6PD deficiency (resistance to malaria), defects in any one of the four P450 genes that cause congenital adrenal hyperplasia (protection against *Hemophilus influenzae* B infections), high pepsinogen I in gastric secretions (resistance to tuberculosis), idiopathic hemochromatosis (protection against iron loss, such as that during menses), and cystic fibrosis (possible resistance to cholera toxin and/or bronchial asthma). On the basis of the earlier discussion in this editorial—noting that DMEs are evolutionarily very old enzymes that are responsible for numerous critical life functions—it is conceivable that at least some of the human DME allelic differences might represent balanced polymorphisms that we presently cannot appreciate, such as improved rates of implantation, prenatal growth, postnatal development in response to dietary selective pressures, or even resistance to bacterial or viral infections (Diamond 1987; Gonzalez and Nebert 1990).

Conclusions

It is clear that DMEs first evolved for critical life functions and that then, in animals, DMEs more recently expanded to include the role of detoxification of dietary products, evolving plant metabolites, and, of course, drugs. A more appropriate name for DMEs therefore might be "effector-metabolizing enzymes." Many human DME polymorphisms, including the *CYP2D6* polymorphism described in this issue of the *Journal* (Sachse et al. 1997), are relevant to clinical problems in that they represent the basis of risk factors in the development of cancer and other diseases associated with drug or chemical exposure. The study of the relationship between genetic polymorphisms, cancer susceptibility, toxicity, and environmental exposure is a new and exciting area of research—which undoubtedly will have important implications for the prevention, early diagnosis, and intervention of human disease.

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